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Regulation of metabolism by sirtuins

Marcia Haigis

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Mitochondrial sirtuins are NAD-dependent enzymes that bind and regulate numerous metabolic pathways within the mitochondria. For example, SIRT3 functions as an NAD-dependent deacetylase that binds and activates numerous oxidative pathways. We have discovered that sirtuins regulate metabolic pathways important in tumor cell metabolism. One hallmark feature of tumor cells is a shift from oxidative to glycolytic metabolism, and this reliance on aerobic glycolysis to support cell growth is known as the Warburg effect. We have discovered that SIRT3 has an additional effect on cellular metabolism by repressing cellular glycolysis through the regulation of HIF1 α , a transcription factor that increases gene expression of glycolytic targets. SIRT3 null cells exhibit metabolic and genetic features of the Warburg effect and enhanced tumorigenicity *in vivo*. Likewise, SIRT3 overexpression reduces glycolysis in tumor cells. In sum, a better understanding of sirtuin-mediated regulation may identify novel ways to therapeutically target tumor metabolism.

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